Addition of a Selective 5-HT_{2A}/D_4 Antagonist Accelerates the Antidepressant Effects of Citalopram

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Improvement in symptoms of depression is typically delayed with antidepressant treatment, and that delay is associated with prolonged morbidity, increased risk for suicide and substance abuse, decreased compliance, and early treatment discontinuation. One theory for the delay in clinical response is that stimulation of 5-HT_{2A} receptors induces a temporary feedback loop, reducing the effect of increased serotonin at the synapse. This raises the possibility of increasing the early efficacy of selective serotonin reuptake inhibitors (SSRIs) by blocking this mechanism. Pipamperone (PIP) at very low doses acts as a highly selective 5-HT_{2A}/D_4 receptor antagonist. The purpose of this 8-week, double-blind, parallel-group, single-dummy study was to investigate whether the addition of PIP 5 mg BID to citalopram (CIT) 40 mg daily (PIPCIT) would increase the rate of resolution of depressive symptoms. The mean total Montgomery-Asberg Depression Rating Scale (MADRS) score (SD) of the 165 patients (81% women; mean age, 40 y; mean body weight, 80 kg) was 32.6 (5.5). More CIT than PIPCIT patients discontinued treatment in the first 4 weeks (15 [18%] vs 3 [4%]; P=0.003). Reductions in mean total MADRS scores were significantly (intent to treat; last observation carried forward) larger in patients receiving PIPCIT after 1 week (–6.42 [6.18] vs –3.99 [5.15]; P=0.007) and 4 weeks (–15.06 [8.48] vs –12.11 [8.30]; P=0.025) compared with those receiving CIT alone. Significant differences in favor of PIPCIT were observed in MADRS items "reduced sleep," "reduced appetite," "concentration difficulties," and "pessimistic thoughts." Mean Clinical Global Impression–Improvement (CGI-I) scores were also improved after 1 week of PIPCIT (3.09 [0.85] vs 3.47 [0.72]; P=0.002). There were no significant differences observed at 8 weeks. No additional clinically significant adverse events were noted in the PIPCIT group. A very low dose of PIP added to CIT provided superior antidepressant effects and fewer discontinuations compared with CIT alone during the first 4 weeks of treatment, and especially in the first week, at apparently no tolerability/safety cost.

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Introduction

- Many patients with major depressive disorder (MDD) do not demonstrate a clinically significant response to antidepressant drugs until ≥4 weeks after initiation of treatment.[1]
- Slow antidepressant therapeutic effect can reduce compliance and possibly increase the risk for suicide or suicidal behavior[2,3]; early symptom improvement (<4 wk) has been associated with eventual treatment response.[4]
- Serotonin reuptake inhibitors act by preventing the presynaptic reuptake of serotonin, increasing synaptic availability; this results in increased stimulation and desensitization of the postsynaptic 5-HT$_{1A}$ receptor.
- Increased serotonin also stimulates 5-HT$_{2A}$ receptors, leading to inhibition of 5-HT$_{1A}$ receptor stimulation by a negative feedback mechanism.[5]
- Hence, administration of a 5-HT$_{2A}$ antagonist could disinhibit 5-HT$_{1A}$ receptors[5] and speed the therapeutic effect.[6]
  - However, because 5-HT$_{2A}$ antagonism increases dopaminergic neurotransmission, it could precipitate D$_4$ receptor–mediated behavioral dysregulation.
- The mild neuroleptic pipamperone (PIP)—at very low doses not currently used clinically—is a highly selective 5-HT$_{2A}$ and D$_4$ antagonist.[7,8] We hypothesized that administration of PIP with the antidepressant citalopram (CIT) would improve the antidepressant effect and hasten the resolution of symptoms.

Objective

- To investigate whether the addition of PIP 5 mg twice daily (BID) to CIT 40 mg once daily (QD) improves antidepressant efficacy and speeds the rate of resolution of depressive symptoms relative to CIT monotherapy in patients with MDD

Methods

Study Design

- Phase II multicenter, randomized, double-blind, parallel-group, placebo-controlled study with 8-week treatment phase and 4-week safety follow-up
  - This report includes only secondary outcomes.

Main Inclusion Criteria

- Men and women 18–65 years of age with moderate to severe MDD according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)
- Current nonpsychotic depressed episode lasting 4–26 weeks
- Clinical Global Impression–Severity of Illness scale rating ≥4 and Hamilton Depression Scale ≥18 at screening and baseline

Main Exclusion Criteria

- Significant risk of suicide
- Significant physical or other psychiatric illness that would interfere with study assessments
- Resistant depression
- Use of antidepressants or other psychotropic substances in past week
- Current formal psychotherapy or alternative treatments in past week or during study
- Electroconvulsive therapy during current episode

Treatment

- Patients were randomized in a 1:1 ratio to receive treatment with CIT 40 mg QD plus PIP 5 mg BID (combination termed PIPCIT) or CIT 40 mg QD and placebo BID.

Assessments

- The Montgomery-Asberg Depression Rating Scale (MADRS) was administered at baseline and weeks 1, 2, 4, 6, and 8.
- Clinical Global Impression–Improvement scale (CGI-I) was assessed at weeks 1, 2, 4, 6, and 8.
- Safety assessments included reporting of adverse events (AEs), clinical laboratory evaluation, vital signs, electrocardiogram, and physical examination.

Statistical Analysis

- Analyses were performed using the intent-to-treat (ITT) population, comprising all randomized patients.
- Missing data were imputed using last observation carried forward (LOCF); in addition, a mixed-effects model for repeated measures (MMRM) was used to manage missing data and mitigate LOCF bias.[9]
- Changes in MADRS scores and prolactin levels from baseline were compared between groups using 2-sample *t* tests.
- Treatment effect differences for MADRS and CGI-I scores at weeks 1, 2, 4, 6, and 8 were estimated with MMRM.
- Global treatment effect differences over 4 and 8 weeks were estimated using MMRM.
- MADRS sustained early full response (≥50% improvement from baseline at weeks 2 and 4) was compared using logistic regression.
- Discontinuation rates and AEs were compared using the Fisher exact test.

Results

Patient Characteristics and Discontinuations

- There were 165 patients in the ITT population.
  - 81% of patients were women; mean age was 40 years.
  - Mean duration of the current MDD episode was 97.2 days; mean (SD) total MADRS score was 32.6 (5.5).
  - There were no clinically important group differences in demographic and clinical characteristics **(Table 1)**.

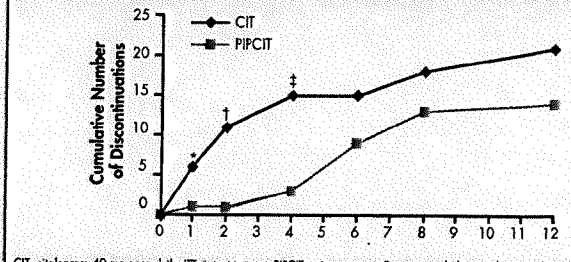
Table 1. Patient Demographics and Clinical Characteristics

	CIT (n=82)	PIPCIT (n=83)
Mean (SD) age, y	39.7 (11.8)	40.1 (11.4)
Sex, n (%)		
Women	63 (77)	70 (84)
Race, n (%)		
White	82 (100)	82 (99)
Black	0	1 (1)
Mean (SD) weight, kg	79.9 (23.7)	80.0 (22.2)
Mean (SD) duration current MDD episode, d	99.6 (43.1)	94.8 (37.7)
n (%) with duration >12 wk	46 (56)	43 (52)
Mean (SD) MADRS total score	32.4 (5.9)	32.7 (5.1)
n (%) with MADRS ≥30 (severe depression)	58 (71)	57 (69)
Mean (SD) score MADRS item 9: pessimistic thoughts	3.1 (1.0)	2.9 (1.1)
Mean (SD) score MADRS item 10: suicidal thoughts	1.7 (0.9)	1.6 (0.9)
Other psychiatric history not ongoing, n (%)	53 (65)	65 (78)

CIT=citalopram 40 mg once daily; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; PIPCIT= pipamperone 5 mg twice daily + citalopram 40 mg once daily.

- Of the 165 randomized patients, 26% (21/82) of the CIT group and 17% (14/83) of the PIPCIT group discontinued treatment **(Figure 1)**.
  - More CIT (18% [15/82]) than PIPCIT (4% [3/83]) patients discontinued during the first 4 weeks (P=0.003; Fisher exact test).
  - The most frequent reasons for discontinuation were loss to follow-up (CIT, n=8; PIPCIT, n=6) and unwillingness to continue (CIT, n=5; PIPCIT, n=2).
  - More patients in the CIT group (5% [4/82]) discontinued because of an AE (vs 2% [2/83] with PIPCIT).
  - 1 patient in each group discontinued because of lack of efficacy.
    - Post hoc analysis determined that the mean (SD) change in MADRS score from baseline to week1 was significantly smaller for patients dropping out between weeks 1 and 2 (–0.4 [2.2]; n=5, all CIT group) compared with patients continuing past week 2 (–5.6 [5.8]; n=152; P=0.01; Wilcoxon test).

Figure 1. Cumulative Number of Discontinuations by Week of Clinic Visit (ITT)



CIT=citalopram 40 mg once daily; ITT=intent to treat; PIPCIT= pipamperone 5 mg twice daily + citalopram 40 mg once daily.
*P=0.06.
†P=0.002
‡P=0.003

Concomitant Medication and Treatment Compliance

- Concomitant medications taken by >10% of patients were analgesics (55%), sex hormones and modulators of the genital system (22%), drugs for acid-related disorders (22%), systemic antibacterial agents (19%), anti-inflammatory drugs (18%), and drugs for asthma or other obstructive airway diseases (17%).
- In both treatment groups, treatment compliance was >95%.

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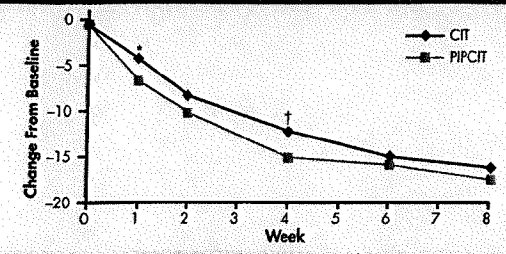
MADRS Scores

- There was significantly greater improvement in mean (SD) MADRS total score from baseline with PIPCIT vs CIT at week 1 (–6.4 [6.2] vs –4.0 [5.2], respectively; *P*=0.007) and week 4 (–15.1 [8.5] vs –12.1 [8.3]; *P*=0.03, ITT, LOCF) **(Figure 2)** but no difference between groups at week 8 (–17.5 [10.1]vs –16.2 [10.6]; *P*=0.40, ITT, LOCF).

Figure 2. Change From Baseline in MADRS Total Scores Over Time (ITT, LOCF)



CIT=citalopram 40 mg once daily; ITT=intent to treat; LOCF=last observation carried forward; MADRS=Montgomery-Asberg Depression Rating Scale; PIPCIT=pipamperone 5 mg twice daily + citalopram 40 mg once daily.
*P=0.007.
†P=0.03.

- Mean (SD) MADRS scores were significantly lower with PIPCIT vs CIT at week 1 (26.3 [7.3] vs 28.4 [7.0], respectively; *P*=0.05, ITT, LOCF) and week 4 (17.6 [8.8] vs 20.3 [9.6]; *P*=0.02, ITT, LOCF).
- In the ITT/LOCF analysis, PIPCIT produced a superior global treatment effect for the MADRS total score over the first 4 weeks and for the MADRS items "reduced sleep," "reduced appetite," "concentration difficulties," and "pessimistic thoughts" over the first 4 weeks and full 8 weeks **(Table 2)**.
  - There was a nonsignificant difference in global treatment effect over 8 weeks favoring PIPCIT **(Table 2)**.

Table 2. Global Treatment Effect Difference Between PIPCIT and CIT for MADRS Total and Item Scores (ITT, LOCF)

	Global Treatment Effect Difference (95% CI) PIPCIT – CIT			
	4 wk	*P* Value	8 wk	*P* Value
MADRS total score	–2.6 (–4.4 to –0.9)	0.004	–1.9 (–3.8 to 0.1)	0.06
MADRS items				
Reduced sleep	–0.7 (–1.0 to –0.3)	<0.001	–0.6 (–0.9 to –0.2)	0.001
Reduced appetite	–0.4 (–0.7 to –0.1)	0.02	–0.3 (–0.6 to 0)	0.05
Concentration difficulties	–0.3 (–0.5 to –0.1)	0.01	–0.2 (–0.5 to 0)	0.05
Pessimistic thoughts	–0.2 (–0.5 to 0)	0.05	–0.3 (–0.5 to –0.1)	0.02

CIT=citalopram 40 mg once daily; ITT=intent to treat; LOCF=last observation carried forward; MADRS=Montgomery-Asberg Depression Rating Scale; PIPCIT=pipamperone 5 mg twice daily + citalopram 40 mg once daily.

- In the MMRM analysis of the ITT population, PIPCIT produced a superior global treatment effect for the MADRS items "reduced sleep" (4 wk and 8 wk) and "reduced appetite" (4 wk) **(Table 3)**.
- There was a significantly better early full response with PIPCIT (21% [17/80]) vs CIT (9% [6/67]; *P*=0.05, ITT).

Table 3. Global Treatment Effect Difference Between PIPCIT and CIT for MADRS Total and Item Scores (ITT, MMRM)

	Global Treatment Effect Difference (95% CI) PIPCIT – CIT			
	4 wk	*P* Value	8 wk	*P* Value
MADRS total score	–1.6 (–3.3 to 0.1)	0.07	–0.5 (–2.3 to 1.3)	0.57
MADRS items				
Reduced sleep	–0.6 (–0.9 to –0.2)	0.002	–0.4 (–0.8 to –0.1)	0.02
Reduced appetite	–0.3 (–0.7 to 0.0)	0.04	–0.2 (–0.5 to 0.1)	0.17

CIT=citalopram 40 mg once daily; ITT=intent to treat; MADRS=Montgomery-Asberg Depression Rating Scale; MMRM=mixed-effect model for repeated measures; PIPCIT=pipamperone 5 mg twice daily + citalopram 40 mg once daily.

CGI-I Scores

- At week 1, mean (SD) CGI-I scores were significantly lower with PIPCIT (3.1 [0.9]) vs CIT (3.5 [0.7]; *P*=0.01, ITT, LOCF; linear regression estimate of treatment effect difference, –0.4; 95% CI, –0.7 to –0.1; *P*=0.004).

Safety

- AEs were reported by 84% (67/80) of the CIT group and 93% (77/83) of the PIPCIT group (*P*=0.09, Fisher exact test).
- Reporting of common AEs was generally similar between groups **(Table 4)**; the most frequently reported AEs were gastrointestinal disorders and nervous system disorders.
- Mean (SD) serum prolactin elevation from baseline to week 8 was significantly greater with PIPCIT (3.8 ng/mL [5.5]) compared with CIT (0.7 ng/mL [6.0]; *P*=0.003, *t* test), but there were no cases of hyperprolactinemia at week 8.
- There were no clinically relevant group differences in other laboratory results, vital signs, or electrocardiogram.
- Body weight was greater in the PIPCIT vs CIT group from week 2–8 (global treatment effect difference over 8 wk, 0.9; 95% CI, 0.4–1.4; *P*=0.001, ITT); this was mainly driven by a greater weight reduction in the CIT group.

Table 4. Common Adverse Events (Occurring in ≥5% of Patients in Either Group) in the Safety Population

Adverse Event, n (%)	CIT (n=80)	PIPCIT (n=83)
Nausea	26 (33)	19 (23)
Headache	19 (24)	21 (25)
Diarrhea	13 (16)	10 (12)
Dry mouth	6 (8)	12 (15)
Fatigue	8 (10)	9 (11)
Hyperhidrosis	9 (11)	7 (8)
Upper respiratory tract infection	9 (11)	6 (7)
Dizziness	6 (8)	8 (10)
Nasopharyngitis	7 (9)	5 (6)
Tremor	4 (5)	6 (7)
Vomiting	4 (5)	5 (6)
Night sweats	2 (3)	7 (8)
Cough	3 (4)	5 (6)
Lower respiratory tract infection	3 (4)	4 (5)
Influenza	2 (3)	4 (5)
Somnolence	1 (1)	6 (7)
Lethargy	4 (5)	2 (2)
Rash	4 (5)	2 (2)

CIT=citalopram 40 mg once daily; PIPCIT= pipamperone 5 mg twice daily + citalopram 40 mg once daily.

Conclusions

- **In this randomized controlled trial in patients with MDD, addition of low-dose PIP to CIT accelerated the clinical response compared with CIT monotherapy.**
- **At 1 week of treatment, PIPCIT produced a significantly greater improvement in MADRS symptoms from baseline compared with CIT monotherapy.**
- **PIPCIT also produced a superior global treatment effect on the MADRS during the first 4 weeks of the trial and significantly lower CGI-I scores at week 1 of treatment; PIPCIT was numerically superior on MADRS change over 8 weeks but just failed to reach statistical significance.**
- **The addition of PIP to CIT did not result in a different tolerability/safety profile.**
- **The observed lower discontinuation rate with PIPCIT vs CIT in the first weeks may be associated with a more rapid resolution of depressive symptoms in patients with MDD.**

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